

EXHIBIT A



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|-----------------|-------------|----------------------|---------------------|
| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY/DOCKET NO. |
| 087558,303 | 11/15/95 | LIVAK | 18M2/0121 |

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| EXAMINER |
| NEBO, D |

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| ART UNIT | PAPER NUMBER |
| 1007 | |

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// 01/21/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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|------------------------------|--------------------------------------|-------------------------------------|
| Office Action Summary | Application No. 08/558,303 | Applicant(s) Livak et al. |
| | Examiner Dianne Rees | Group Art Unit 1807 |

☒ Responsive to communication(s) filed on 2/1/96, 5/13/96, 5/25/96, 10/25/96, 11/5/96, 11/22/96.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-40 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-40 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5,6,10

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Serial Number: 08558303

Page 2

Art Unit: 1807

DETAILED ACTION

Priority

Applicant is reminded to update the status of the parent application in the first paragraph of the specification.

Information Disclosure Statement

1. The information disclosure statement filed 11/22/96 (reference JP5123195) fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered

Serial Number: 08558303

Page 3

Art Unit: 1807

Specification

2. The disclosure is objected to because of the following informalities: The specification contains matter presented in the form of Tables which should properly be presented as drawings (See Tables 2-4; arrows and curved lines will not be able to be reproduced by the printer in the body of the specification). Further, said Tables contain alterations , "Fmoc", for example, which are not initialled ^{and} ~~is~~ dated. Upon submitting these Tables as Figures, Applicant is reminded to amend the Brief Description of the drawings and the remainder of the specification appropriately. ^{10/1/97}

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. Claims 1-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following phrases render the claims vague and indefinite:

a. In claim 1, the recitation of " conditions favorable for hybridization" renders the claim indefinite since as the specificity of hybridization is not recited it is unclear what the metes and bounds of these conditions are. The claim is further indefinite in the recitation of "said

Serial Number: 08558303

Page 4

Art Unit: 1807

oligonucleotide probe including an oligonucleotide sequence capable of hybridizing to said target polynucleotide to be detected that does not hybridize with itself". It is unclear whether "itself" refers to the sequence included within the probe or the entire probe sequence. If the former is true does the claim encompass sequences outside the sequence which may potentially form a hairpin? The claim is further indefinite in that it is unclear how the sequence "includes" a reporter molecule and a quencher molecule (are they attached to the sequence?). The claim additionally appears to be missing words on page 2, between "unquenched" and "the fluorescent intensity" (an --and-- or --wherein--?). See all independent claims for examples of this language.

b. Claim 13 is indefinite in the recitation of "The method according to claim 1, wherein said nucleic acid polymerase is a thermostable nucleic acid polymerase" since claim 1 did not recite a nucleic acid polymerase.

c. Claim 17 is indefinite in the recitation of the ratio of fluorescent intensities of said reporter molecule to said quencher molecule" in that the quencher molecule in this claim was not recited as being fluorescent so it is unclear what "intensities" are actually being compared to arrive at a ratio. See claims 18, 39, and 40.

Claim Rejections - 35 USC § 102

Serial Number: 08558303

Page 5

Art Unit: 1807

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 15, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Heller et al.(EPO 0 229 943, 1987).

Heller teaches the use of fluorescent probes in a polynucleotide hybridization assays comprising donor and acceptor fluorophores (interpreted as a quencher fluorophore).. Maximum observed acceptor fluorophore emission was also found to be dependent upon hybridization of the probe to its complementary target sequence (page 6, lines 29-31). With proper spacing between fluorophores an exceptionally high value for fluorescent emission by the acceptor fluorophore can be obtained (pages 6-7, pages 7-8) (any increase observed could be interpreted as meeting the limitation of "at least by *about* a factor of 6" or at "least *about* a factor of 3.5").

Claims 1-16, are rejected under 35 U.S.C. 102(b) as being anticipated by Bagwell (EPO 601 889 A2 1994). Bagwell teaches a probe which includes an oligonucleotide sequence, at least one donor label molecule and at least one acceptor label molecule . The donor and acceptors are taught as preferentially being fluorophores (see abstract and page 4, lines 20-48). Bagwell further teaches methods of using these probes in which the labeled probe exhibits different characteristics

Serial Number: 08558303

Page 6

Art Unit: 1807

when associated with a target (i.e hybridized) that when unassociated (i.e unhybridized) (see pages 3-4). Although Bagwell's probe has hairpin sequences within it, the probe also includes a sequence which binds to a target and does not bind "to itself" (the specificity sequence), rather it binds to the "competitive arm" portion of the probe. The reporter and quencher molecules are taught as being at the 5' and 3 terminal nucleotides of the probe and may be at least 18 nucleotides apart. The increase in fluorescent intensity observed upon binding is at least a factor of about six (see Figure 9).

Claims 1 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by HITACHI LTD (JP 5123195, abstract).

HITACHI LTD teaches a method of detecting a polynucleotide in a sample which comprises providing a probe with an energy donor and an energy receptor (interpreted as meaning a quencher molecule) is provided. The probe hybridizes with a target nucleic acid sample and the energy transfer obtained when the hybrid forms is detected.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Serial Number: 08558303

Page 7

Art Unit: 1807

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14,17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller or Bagwell.

Heller or Bagwell et al. meet all of the limitations of the claims except for the teaching of a reporter quencher pair which is fluorescein and rhodamine, determining a ratio of the fluorescent intensity of the reporter vs, the quencher molecule when the probe is in a hybridized vs an unhybridized state. However the suitability of fluorescein and rhodamine as donor-quencher molecules was well known in the art at the time that the invention was made therefore it would have been prima facie obvious in view of Heller's general teaching of the use of "fluorophores" to select the species of fluorescein and rhodamine, given that these would be functionally equivalent

Serial Number: 08558303

Page 8

Art Unit: 1807

to the fluorophores taught by Heller. Further, absent any evidence to the contrary, given that determining the ratio of intensity of reporter molecules and quencher molecules represents simply another method of interpreting the data obtained from the method of Heller or Bagwell, it would have been *prima facie* obvious to one of ordinary skill in the art at the time that the invention was made to measure such ratios as another means of expressing how much quenching had actually occurred. One would be motivated to do so for the expected benefit of having a set of data points that would indicate the degree of hybridization that had occurred.

Claims 19-20, 32-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller in view of Sheriden et al (WO 93/13224).

Heller meets all of the limitations of the claims as discussed above except for the teachings that the probes are immobilized on a solid support.

However, Sheriden et al. teaches nucleic acid probes that are immobilized on a solid support such as wells of microtiter plates for use in solution phase nucleic acid sandwich hybridization assays. Sheriden further teaches that these probes can be labeled with in ore more labels which may directly or indirectly provide for a detectable signal. Sheriden further teaches that a variety of linkers may be used as a means of attaching the probe to the support. One would have been motivated to modify the method of Heller by immobilizing the probes of Heller on a solid support to carry out a hybridization assay to obtain the expected benefits taught by Sheriden of improved reproducibility of the assay and reduced background signal. (page 2, lines 26-29).

Serial Number: 08558303

Page 9

Art Unit: 1807

Claims 19-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bagwell in view of Sheriden et al (WO 93/13224).

Bagwell et al meets all of the limitations of the claims as discussed above except for the teachings that the probes are immobilized on a solid support.

However, Sheriden et al. teaches nucleic acid probes that are immobilized on a solid support such as wells of microtiter plates for use in solution phase nucleic acid sandwich hybridization assays. Sheriden further teaches that these probes can be labeled with in one more labels which may directly or indirectly provide for a detectable signal. Sheriden further teaches that a variety of linkers may be used as a means of attaching the probe to the support. One would have been motivated to modify the method of Heller by immobilizing the probes of Heller on a solid support to carry out a hybridization assay to obtain the expected benefits taught by Sheriden of improved reproducibility of the assay and reduced background signal. (page 2, lines 26-29).

No claims are allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 305-7401. Please note that the faxing of such papers must conform with the notice to Comply published in the Official Gazette, 1096 OG 30 (Nov 15, 1989).

Serial Number: 08558303

Page 10

Art Unit: 1807

An inquiry regarding this communication should be directed to examiner Dianne Rees, Ph.D., whose telephone number is (703)308-6565. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Calls of a general nature may be directed to the Group receptionist who may be reached at (703) 308-0196.

Dianne Rees

W. Gary Jones
W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800
1/15/97